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Original Research

Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma

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Abstract ***Background:*** In KEYNOTE-002, pembrolizumab significantly prolonged progression-free survival and was associated with a better safety profile compared with chemotherapy in patients with advanced melanoma that progressed after ipilimumab. We present health-related quality of life (HRQoL) outcomes from KEYNOTE-002.
Methods: Patients were randomly assigned 1:1:1 to pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or investigator-choice chemotherapy. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 instrument. A constrained longitudinal data analysis model was implemented to assess between-arm differences in HRQoL scores. The study is registered with ClinicalTrials.gov, number NCT01704287.
Results: Of the 540 patients enrolled, 520 were included in the HRQoL analysis. Baseline global health status (GHS) was similar across treatment arms. Compliance rates at week 12 were 76.6% ($n = 108$), 82.3% ($n = 121$), and 86.4% ($n = 133$) for the control, pembrolizumab 2 mg/kg Q3W, and pembrolizumab 10 mg/kg Q3W arms, respectively. From baseline to week 12, GHS/HRQoL scores were maintained to a higher degree in the pembrolizumab arms compared with the chemotherapy arm (decrease of −2.6 for each pembrolizumab arm versus −9.1 for chemotherapy; $P = 0.01$ for each pembrolizumab arm versus chemotherapy). Fewer patients treated with pembrolizumab experienced deterioration in GHS at week 12 (31.8% for pembrolizumab 2 mg/kg, 26.6% for 10 mg/kg, and 38.3% for chemotherapy), with similar trends observed for the individual functioning and symptoms scales.
Conclusions: HRQoL was better maintained with pembrolizumab than with chemotherapy in KEYNOTE-002, supporting the use of pembrolizumab in patients with ipilimumab-refractory melanoma.

1. Introduction

Engagement between the programmed death 1 (PD-1) receptor and its ligands, PD-L1 and PD-L2 [1], inhibits T-cell-receptor signalling, ultimately leading to down-regulation of the T-cell-mediated antitumour immune response [2–4]. The expression of PD-1 ligands by some tumours enables them to avoid surveillance and thus destruction by the innate immune system [5].

PD-1 inhibitors have shown promising activity against a growing list of cancer types [6]. Pembrolizumab and nivolumab are approved anti-PD-1 therapies for the treatment of advanced melanoma [7]. Pembrolizumab, a monoclonal antibody that directly blocks binding between PD-1 and PD-L1/PD-L2 [8], is approved worldwide for the treatment of patients with unresectable or metastatic melanoma, in the United States and European Union for patients with metastatic, PD-L1-expressing non-small-cell lung cancer, and in the United States for recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy [8,9]. Pembrolizumab first demonstrated durable antitumour activity and manageable safety in patients with ipilimumab-naive and ipilimumab-treated advanced melanoma in the phase Ib KEYNOTE-001 study [10]. In the subsequent phase II KEYNOTE-002 trial of patients with advanced melanoma who progressed on ipilimumab and, if $BRAF^{V600}$ mutant, a BRAF and/or MEK inhibitor, pembrolizumab significantly prolonged progression-free survival (PFS) compared with investigator-choice chemotherapy [11]. In the phase III KEYNOTE-006 study, pembrolizumab provided superior overall survival (OS) and PFS and improved safety compared with ipilimumab in patients with ipilimumab-naive advanced melanoma who received one or no prior therapy [12]. These findings led to the approval of pembrolizumab worldwide for both ipilimumab-refractory and ipilimumab-naive melanoma. Nivolumab is also approved worldwide for advanced melanoma on the basis of phase III trials in patients with ipilimumab-refractory [13] and ipilimumab-naive [14,15] metastatic melanoma.

Although outcomes for cancer patients are generally measured in terms of survival and response, patient-reported outcomes (PROs) and health-related quality of life (HRQoL) are of high relevance to the patient [16]. Here, we report analyses of HRQoL for patients with

advanced melanoma treated with pembrolizumab compared with investigator's choice of chemotherapy in KEYNOTE-002.

2. Methods

2.1. Study design

Details of the international, randomised phase II KEYNOTE-002 study (ClinicalTrials.gov, number NCT01704287) were published previously [11]. Briefly, patients with unresectable stage III or IV melanoma, disease progression after two or more prior ipilimumab doses, and previous BRAF and/or MEK inhibitor therapy ($BRAF^{V600}$ mutant only) were randomly allocated 1:1:1 to pembrolizumab 2 mg/kg every 3 weeks (Q3W), pembrolizumab 10 mg/kg Q3W, or investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, dacarbazine, carboplatin, or temozolomide). Treatment was continued until disease progression, unacceptable toxicity, or other reason.

2.2. Assessments

Tumour response was assessed at baseline, at week 12, then every 6 weeks until week 48, and every 12 weeks thereafter per Response Evaluation Criteria In Solid Tumours, version 1.1 (RECIST v1.1), by central imaging vendor review. All patients completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 instrument (QLQ-C30) before all clinical procedures at baseline, weeks 3, 6, 12, 24, and 36, at treatment discontinuation, and during safety follow-up.

2.3. Statistical analyses

PROs were an exploratory end-point with a prespecified statistical analysis before database lock. Analyses were performed in patients who received one or more doses of study medication and who completed one or more PRO assessments (PRO full analysis set [FAS]). An instrument was considered complete if at least one valid score was available. The PRO compliance rate was defined as the proportion of patients who completed the instrument among those expected to complete it at each visit, excluding those missing by design (e.g. death, discontinuation of treatment, instrument translations not available, or no visit scheduled). The PRO completion rate was defined as the proportion of patients who completed the instrument among the PRO FAS population.

Because >50% of patients in the control group were expected to have disease progression at week 12 based on historical data, PRO score changes from baseline were evaluated at week 12. Linear transformation was applied to standardise raw scores to a range of 0–100. A score change of at least 10 points was considered clinically meaningful and was used to define deterioration and improvement [17]. A constrained longitudinal data analysis model was used to assess the effect of treatment and disease progression on PRO score changes. The primary statistical method was a mixed-effect model with multiple imputation based on the missing at random assumption, with sensitivity analysis based on missing pattern and control-based multiple imputation. A summary of the proportion of patients with improvement, stability, and deterioration in global health status (GHS)/HRQoL was also based on the missing at random assumption.

3. Results

3.1. Patients

In total, 540 patients were randomly assigned to pembrolizumab 2 mg/kg ($n = 180$), pembrolizumab 10 mg/kg ($n = 181$), or chemotherapy ($n = 179$). Patient baseline characteristics, which have been published in detail elsewhere [11], were well balanced across the three arms. In brief, patients ranged in age between 15 and 89 years, with a median of 62, 60, and 63 years for the pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy arms, respectively, and a male:female ratio of 1.4, 1.5, and 1.8, respectively. The proportions of patients were similar between the arms for Eastern Cooperative Oncology Group performance status 0 (54%, 54%, and 55%) and presence of $BRAF^{V600}$ mutation (24%, 22%, and 23%).

3.2. Completion and compliance rate of the EORTC QLQ-C30

Of the 540 patients enrolled, 520 received ≥1 dose of study treatment and completed the EORTC QLQ-C30 at least once and were eligible for analysis: 176 in the pembrolizumab 2 mg/kg arm, 177 in the pembrolizumab 10 mg/kg arm, and 167 in the chemotherapy arm. The EORTC QLQ-C30 completion rate decreased over time, along with the number of patients available to complete for all three treatment arms (Table 1). The most common reasons for non-completion were discontinuation because of disease progression or adverse events (AEs), death, and site administrative error (Supplemental Table 1). A higher proportion of patients in the chemotherapy arm did not complete the questionnaire at weeks 3, 6, and 12 because of disease progression.

Compliance rates for the control, pembrolizumab 2 mg/kg Q3W, and pembrolizumab 10 mg/kg Q3W arms were 93.4% ($n = 156$), 96.0% ($n = 169$), and 96.0% ($n = 170$), respectively, at baseline, and 76.6% ($n = 108$), 82.3% ($n = 121$), and 86.4% ($n = 133$) at week 12. Compliance rates decreased in all groups at weeks 24 and 36, particularly among the control group (Table 1 and Supplemental Table 1).

Table 1
The rate of compliance[a] and number of patients available to complete the EORTC QLQ-C30 instrument at each visit.

Time point	Category	Pembrolizumab 2 mg/kg Q3W (n = 176)	Pembrolizumab 10 mg/kg Q3W (n = 177)	Chemotherapy (n = 167)
Baseline	Expected to complete, n	176	177	167
	Completed, n	169	170	156
	Compliance rate in those expected to complete, %	96.0	96.0	93.4
	Completion rate in total population, %	96.0	96.0	93.4
Week 3	Expected to complete, n	172	174	163
	Completed, n	161	157	133
	Compliance rate in those expected to complete, %	93.6	90.2	81.6
	Completion rate in total population, %	91.5	88.7	79.6
Week 6	Expected to complete, n	162	165	151
	Completed, n	144	146	122
	Compliance rate in those expected to complete, %	88.9	88.5	80.8
	Completion rate in total population, %	81.8	82.5	73.1
Week 12	Expected to complete, n	147	154	141
	Completed, n	121	133	108
	Compliance rate in those expected to complete, %	82.3	86.4	76.6
	Completion rate in total population, %	68.8	75.1	64.7
Week 24	Expected to complete, n	104	112	109
	Completed, n	82	101	37
	Compliance rate in those expected to complete, %	78.8	90.2	33.9
	Completion rate in total population, %	46.6	57.1	22.2
Week 36	Expected to complete, n	69	75	72
	Completed, n	33	39	21
	Compliance rate in those expected to complete, %	47.8	52.0	29.2
	Completion rate in total population, %	18.8	22.0	12.6

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30; Q3W, every 3 weeks.
[a] Compliance was defined as the proportion of patients who completed the EORTC QLQ-C30 among those who were expected to complete it at each visit, excluding those missing by design (e.g. death, discontinuation due to an adverse event).

Table 2
Baseline and week 12 global health status scale scores of the EORTC QLQ-C30 and change from baseline at week 12.

Treatment arm	Baseline		Week 12		Change from baseline least squares mean (95% CI)
	n	Mean ± SD	n	Mean ± SD	
Pembrolizumab 2 mg/kg Q3W	169	66.2 ± 22.1	120	66.3 ± 23.0	−2.6 (−6.2, 1.0)[a]
Pembrolizumab 10 mg/kg Q3W	168	62.9 ± 23.6	132	64.3 ± 22.8	−2.6 (−6.0, 0.9)[a]
Chemotherapy	155	64.0 ± 21.9	108	59.0 ± 23.2	−9.1 (−12.9, −5.4)

CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30; Q3W, every 3 weeks; SD, standard deviation.
[a] P = 0.01 versus chemotherapy.

3.3. Change from baseline in HRQoL at week 12

The baseline GHS/HRQoL score was similar across the three treatment arms (mean 66.2, 62.9, and 64.0 in the pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy arms, respectively) (Table 2). Treatment with pembrolizumab resulted in significantly smaller decrements in the GHS/HRQoL scale score compared with chemotherapy, with no difference between pembrolizumab arms (Table 2). The least squares mean (95% confidence interval) change from baseline at week 12 was −2.6 (−6.15 to 0.96) for pembrolizumab 2 mg/kg, −2.6 (−5.99 to 0.89) for pembrolizumab 10 mg/kg, and −9.1 (−12.86 to −5.39) for chemotherapy (Table 2). The differences between pembrolizumab and chemotherapy were statistically significant (P = 0.011 for pembrolizumab 2 mg/kg versus chemotherapy and 0.009 for pembrolizumab 10 mg/kg versus chemotherapy) (Table 2). A similar trend of score change differences was observed in a sensitivity analysis, in which the imputation rule was based on the reason for missingness or control-based multiple imputation (data not shown).

In addition to the GHS/HRQoL score, patients in the two pembrolizumab arms had consistently smaller longitudinal score changes from baseline to week 12 across functional scales, including physical, role, cognitive, social, and emotional functions, and across symptoms scales including fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea (Table 3).

Table 3
Change from baseline to week 12 in scores for the GHS/quality of life and functional and symptom scales of the EORTC QLQ-C30 questionnaire for the full analysis set population.[a]

	Pembrolizumab 2 mg/kg Q3W (n = 176)			Pembrolizumab 10 mg/kg Q3W (n = 177)			Chemotherapy (n = 167)		
	Mean	Upper limit	Lower limit	Mean	Upper limit	Lower limit	Mean	Upper limit	Lower limit
GHS and functional scales									
GHS/quality of life	−2.6	1.0	−6.1	−2.6	0.9	−6.0	−9.1	−5.4	−12.9
Physical functioning	−4.2	−1.0	−7.5	−2.8	0.4	−5.9	−5.2	−1.8	−8.6
Role functioning	−4.7	−0.2	−9.3	−5.8	−1.3	−10.2	−9.3	−4.5	−14.1
Emotional functioning	0.2	3.3	−2.9	0.60	3.6	−2.4	−1.1	2.2	−4.4
Cognitive functioning	−2.1	0.8	−5.1	−1.4	1.5	−4.2	−3.5	−0.4	−6.6
Social functioning	−2.7	1.3	−6.7	−2.4	1.5	−6.3	−4.7	−0.5	−8.9
Symptom scales									
Fatigue	3.3	7.1	−0.5	4.7	8.4	1.0	7.0	11.0	3.0
Nausea and vomiting	1.5	4.3	−1.2	1.4	4.0	−1.3	5.2	8.1	2.3
Pain	0.8	4.9	−3.2	1.2	5.0	−2.7	3.4	7.7	−0.8
Dyspnoea	1.7	5.8	−2.5	−0.1	3.9	−4.1	6.8	11.2	2.5
Insomnia	−0.6	4.1	−5.4	1.5	6.0	−3.1	2.2	7.2	−2.8
Appetite loss	−1.7	3.2	−6.6	1.4	6.1	−3.4	3.3	8.4	−1.9
Constipation	2.5	6.7	−1.7	3.9	8.0	−0.1	5.1	9.5	0.6
Diarrhoea	−1.7	1.4	−4.8	0.0	3.0	−2.9	1.4	4.6	−1.9

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30; GHS, global health status; Q3W, every 3 weeks.
[a] For health-related quality of life or functions, a higher score denotes better quality of life or functions and a higher negative score denotes worse quality of life or functions. For symptoms, a higher score denotes worse symptoms and a higher negative score denotes better symptoms.

We also summarised the observed mean GHS/HRQoL score at different time points for each of the treatment groups, without any imputation of missing data (Fig. 1). As with the longitudinal analysis, the baseline GHS/HRQoL score was similar between the three groups. For the control group, the GHS/HRQoL score declined from baseline to week 12; there was a sharp decrease at week 3. For both of the pembrolizumab arms, scores were relatively stable at different time points. Data at weeks 24 and 36 should be interpreted cautiously because of the limited sample size, particularly among the control group. These results were consistent with those of the primary analysis, in which missing data were imputed by missing at random.

3.4. PRO responder analysis at week 12

The rates of improved, stable, or deteriorated HRQoL at week 12, defined as a change from baseline of ≥10 points, are presented in Fig. 2. Approximately 7–12% fewer patients in the pembrolizumab arms

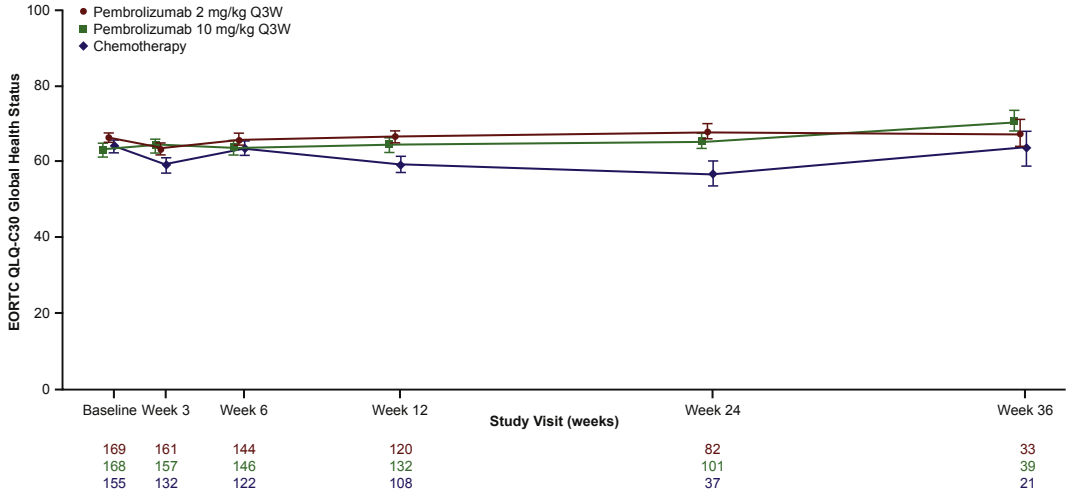

Fig. 1. Sensitivity analysis without imputation of missing data of global health status/health-related quality-of-life score of the EORTC QLQ-C30. The data are presented as mean ± standard error. Abbreviation: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 instrument; Q3W, every 3 weeks.

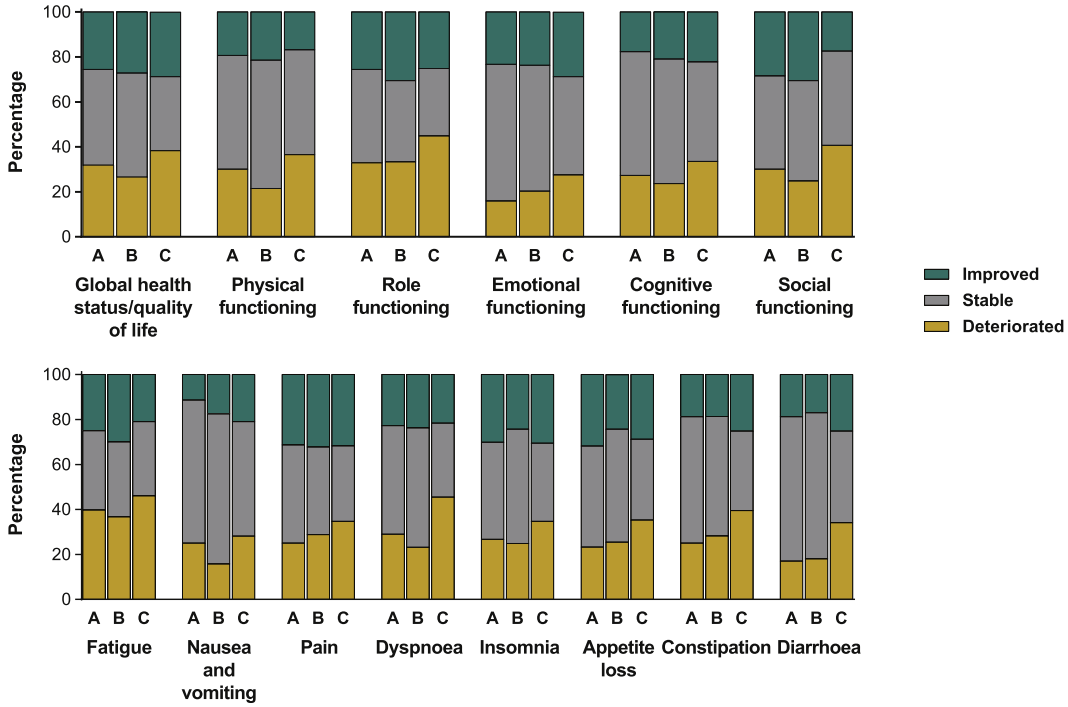

Fig. 2. Proportions of improved, stable, and deteriorated health-related quality of life as assessed by changes from baseline of ≥10 points at week 12 in the global health status and functional and symptom scales of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 instrument. For each plot, A = pembrolizumab 2 mg/kg every 3 weeks (Q3W), B = pembrolizumab 10 mg/kg Q3W, and C = chemotherapy.

reported a deteriorated overall GHS/HRQoL score than in the chemotherapy arm (31.8% in the pembrolizumab 2 mg/kg arm, 26.6% in the pembrolizumab 10 mg/kg arm, and 38.3% in the control arm). The two pembrolizumab arms had consistently smaller proportions of deteriorated and generally larger proportions of stable or improved scores for different functional and symptoms scales compared with the control arm. These responder analyses are consistent with the longitudinal analysis showing that mean GHS/HRQoL is better at week 12 for patients in the pembrolizumab arms compared with the control arm. Similar results were observed at other time points, including weeks 3 and 6 (data not shown). This finding persisted when considering each subdomain separately or when using more stringent thresholds of 15 and 20 points (data not shown).

3.5. 'Progression effect' analysis

Across treatment arms, patients without disease progression had similar GHS/HRQoL scores at baseline and at the most recent assessment before treatment discontinuation (Fig. 3). Conversely, GHS/HRQoL scores decreased by approximately 10 points at the time of discontinuation. Scores were generally worse in the presence of disease progression than in its absence, among the different treatment arms and for the overall population. A similar trend of association was observed when using the observed data without any imputation (Supplemental Fig. 1). These results suggested that disease progression has a negative impact on patients' HRQoL, regardless of the treatment received.

We also performed a *post hoc* analysis of the joint effect of treatment and disease progression on HRQoL.

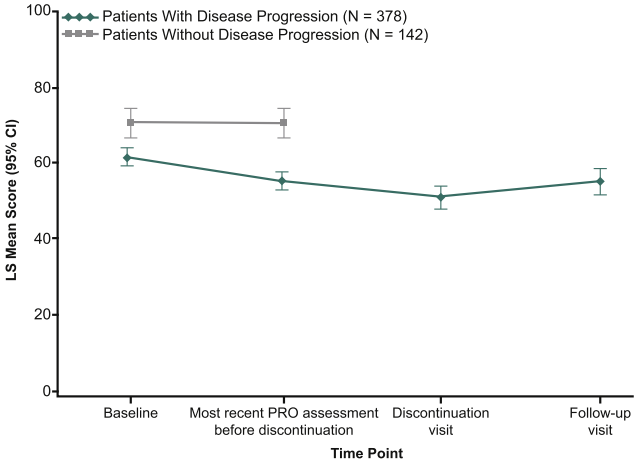

Fig. 3. Global health status/health-related quality-of-life scores of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 instrument over time in patients with and without disease progression. The follow-up visit was 30 d after discontinuation. Abbreviations: LS, least squares; CI, confidence interval; PRO, patient-reported outcome.

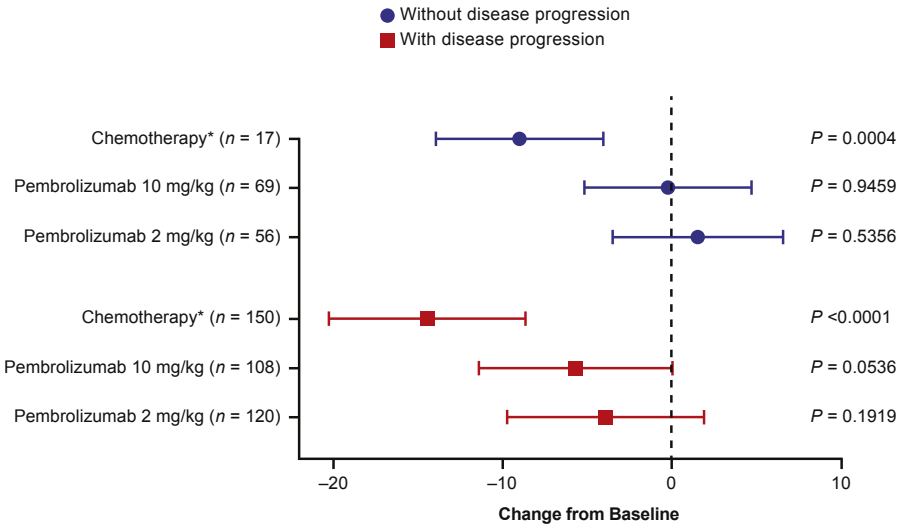

Fig. 4. Impact of disease progression and treatment arm on change from baseline in global health status/health-related quality of life at week 12. *$P < 0.05$ for change from baseline to week 12.

As shown in Fig. 4, both chemotherapy and disease progression had a negative effect on the GHS/HRQoL score, but the decrease was statistically significant for the chemotherapy arm only. Among patients treated with pembrolizumab without progression, there was a minimal change in the GHS/HRQoL score ($P = 0.5356$ for the 2 mg/kg arm; $P = 0.9459$ for the 10 mg/kg arm). For patients treated with chemotherapy, there was an estimated 8.95-point decrease from baseline among patients without progression ($P = 0.0004$) and a 14.4-point decrease among those with progression ($P < 0.0001$). Across treatment arms, disease progression was estimated to induce a 5.46-point decrease in the GHS/HRQoL score from baseline to week 12 ($P = 0.009$).

4. Discussion

For metastatic melanoma, the choice of systemic therapy is influenced not only by efficacy and symptom control but also by HRQoL [18–20]. KEYNOTE-002 enrolled patients with ipilimumab-refractory advanced melanoma, with two-thirds of patients having had at least two previous lines of treatment [11]. The results of the present PRO analysis for KEYNOTE-002 nevertheless indicate that the patients treated with pembrolizumab maintained HRQoL to a greater degree compared with chemotherapy. The results were consistent following sensitivity analyses, including using different imputation methods on missing PRO data and analysing only the observed data at different time points without any imputation. Furthermore, they are supported by the finding that the pembrolizumab-treated patients had consistently smaller score changes from baseline to week 12 for different functional and symptoms scales compared with their chemotherapy-treated counterparts.

In addition, consistently smaller proportions of deteriorated, and larger proportions of stable or improved GHS/HRQoL and functional and symptoms scales scores were observed for the two pembrolizumab arms compared with the chemotherapy arm. GHS/HRQoL deteriorated by ≥10 points in 7–12% fewer patients in the pembrolizumab arms than in the chemotherapy arm between baseline and week 12. These results are consistent with the finding that mean GHS/HRQoL was better at week 12 for pembrolizumab-treated patients than for those on chemotherapy. Finally, disease progression was found to have a negative impact on GHS/HRQoL regardless of the therapeutic modality, as has been described for other systemic therapies [20,21].

Taken together, these findings suggest that pembrolizumab is well tolerated and either improves or maintains HRQoL or symptoms when compared with chemotherapy. Furthermore, they support the reported clinical benefit of pembrolizumab over chemotherapy with respect to PFS [11]. Therefore, delaying disease progression or extending PFS appears to help to maintain or improve HRQoL in these patients.

Associations between improvements in HRQoL and therapeutics that confer survival benefits (PFS and OS) in $BRAF^{V600}$ mutant metastatic melanoma have been reported previously. A better preservation of HRQoL appeared to be associated with delayed disease progression in a phase III study of dabrafenib and trametinib versus dabrafenib monotherapy (the COMBI-d trial) [20], and similar findings were reported in a phase III study of trametinib versus chemotherapy (the METRIC study) [19]. Similarly, in the COMBI-v study of dabrafenib and trametinib versus dabrafenib

monotherapy, the combination therapy was associated with improved HRQoL compared with dabrafenib monotherapy [21].

These and the present findings raise the question of whether PROs can be a surrogate marker for prognosis in the oncology setting. In a global analysis of multitrial data across 11 cancer sites, Quinten *et al.* [22] found that at least one baseline HRQoL domain yielded prognostic information for each cancer site additional to those provided by clinical and sociodemographic variables, suggesting that baseline HRQoL data can add complementary prognostic value to standard clinical variables. In a systematic review of the literature, Montazeri [23] found a significant and positive relationship between certain HRQoL parameters and survival among patients with various cancer types, including melanoma. Further studies are needed to establish a definitive prognostic relationship between HRQoL measures and clinical outcome in advanced melanoma patients treated with pembrolizumab.

4.1. Study limitations

These findings should be considered in the light of several limitations. Firstly, clinical trial populations may differ from melanoma patients in the general population with regard to motivation, the likelihood of PRO reporting, and ability to withstand treatment-related AEs. Secondly, the number of patients without disease progression in the chemotherapy arm was low compared with those without progression in the pembrolizumab arms. Thus, the HRQoL outcomes reported here are likely associated with tumour progression in addition to chemotherapy-related side-effects. Thirdly, this was a partially blinded study; assignment to the chemotherapy arm versus one of the two pembrolizumab arms was open label. However, the PRO results are consistent across different domains and different sensitivity analyses, suggesting the results are unlikely to be biased because of the partially blinded design.

5. Conclusions

HRQoL was maintained to a greater degree with pembrolizumab than with investigator-choice chemotherapy in patients with ipilimumab-refractory melanoma. Approximately 10% more patients treated with chemotherapy than with pembrolizumab experienced deterioration in HRQoL by week 12. Regardless of treatment, HRQoL decreased in patients who experienced disease progression. These data support the use of pembrolizumab in this patient population.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.07.018.

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